Subject: PhRMA Response to the Draft Guidance for Industry on "Nonclinical Safety Evaluation of Drug Combinations", Federal register, Volume 70, No. 16, Pages 3714-3715 (January 26, 2005)

Overview

The Pharmaceutical Research and Manufacturers of America (PhRMA) has had the opportunity to review the draft guidance entitled *"Nonclinical Safety Evaluation of Drug Combinations"*. This draft guidance is timely in its introduction as there is a lack of detailed regulatory guidance on strategies for combination product development. We are pleased in that it provides much needed direction concerning the nonclinical development of drug combinations containing marketed drugs (MD) and/or new molecular entities (NME) and we commend the Food and Drug Administration (FDA) for taking this initiative.

As clearly stated in the document, each drug combination program is unique with regards to its safety concerns and clinical program, and therefore, it is impossible to provide detailed guidance that applies to all development programs. So the flexibility of this guidance and the recommendation for consultation (e.g., pre-IND meeting) with the FDA to obtain more detailed advice for a specific drug combination program is fully endorsed by PhRMA.

PhRMA has the following comments to offer for consideration following review of the draft guidance.

Summary

We commend the FDA for preparing the draft guidance for industry on *"Nonclinical Safety Evaluation of Drug Combinations"* and we generally agree with the guidance as set forth. However, several aspects of the guidance require clarification. We are principally concerned with implications of the combination category "adjunctive therapy". The broad definition seemingly involving any number and any manner of combinations is an impossible situation when considering combination safety testing strategies. To nonclinically assess the safety of all potential adjunctive therapy combinations a physician may prescribe, especially when the combination may not be labeled or developed by the sponsor for concomitant use, is excessive and this aspect of the guidance needs to be redefined.

There is general reference made to study timing, special conditions under which additional studies would be required, and species and dose selection, which require further detail and consistency to be useful to sponsors in designing complex development programs. The willingness on part of FDA to meet and discuss programs is appreciated in this highly complex environment but additional detail and direction would facilitate program design and eliminate the need for multiple iterations of review.

The issue of animal models of efficacy in safety testing is unprecedented and the utility and application of these data to establishing safe dosing limits for clinical studies requires clarification. In general, applicability of these data in species extrapolation is limited and better information would be obtained by targeted preclinical pharmacology studies addressing specific drug targets.

We provide detailed comments and proposals concerning this draft in the sections below.

Detailed Comments

I. Introduction

The definition of adjunctive therapy as given in footnote 2, page 1, is exceedingly broad, and covers situations where any combination of drugs, whether labeled for concomitant use or not, is included. To nonclinically assess the safety of all potential adjunctive therapy combinations a physician may prescribe, especially when the combination may not be labeled or developed by the sponsor for concomitant use, is excessive.

As an alternative, perhaps clinical safety and efficacy for adjunctive therapies could be assessed via drug-drug interaction studies to determine if the efficacy of the primary therapy is altered by common adjunctive therapy for the disease being treated (e.g., effect of a hair growth drug on the efficacy of a chemotherapy drug). Or, possibly, toxicity studies with one molecule from a drug class could be used to evaluate the risk associated with the class in combination with the add-on therapeutic. The molecule selected from the class should have the greatest potential for interaction based on the safety considerations listed in Section II A of the draft guidance. There could be instances where more than one compound from the class met the above criteria and evaluation of more than one compound in toxicity studies might be justified based on diverse pharmacodynamic and/or pharmacokinetic properties.

PhRMA recommends that the conditions and requirements for additional safety testing for adjunctive therapies be refined and that consideration be given to inclusion of an exemption procedure, especially as it applies to products commonly administered with other drugs.

Section II. Nonclinical Studies for a Combination of Two (or more) Previously Marketed Drugs.

A. Safety Considerations

Reference is made to additional nonclinical studies needed to cover data gaps for marketed drugs when usage changes under the combination guidelines (Lines 51 - 53 and 232 - 233). Clarification on this point would be useful, in particular as applies to scenarios requiring carcinogenicity studies and

circumstances where such data are submitted following marketing approval (i.e., Phase IV).

This section (lines 55 -104) lists a series of specific considerations to be taken into account for evaluation of the safety of drug combinations. It would be helpful to provide one or more specific examples to illustrate these considerations.

In lines 83 - 88 reference is made to the effects of combination drugs on established single agent no observed adverse effect levels (NOAEL). If there is an interaction, any single agent NOAEL will be entirely dependent on the ratio of the compounds tested, and therefore has little meaning in the understanding of combination drug safety unless the ratio of the active drug components is constant in all dosage forms. This is a particularly important concept in adjunctive therapy where combinations may vary widely in the absence of detailed labeling. Therefore, establishing a NOAEL in these instances should be secondary in importance to detection and characterization of severe or unexpected toxicity.

"Significant risk" is given as a principal factor in determining the need for combination developmental toxicity studies. Clarification around what constitutes significant risk would be helpful in assessing the need for combination studies.

In lines 177-179, the guidance currently states that carcinogenicity studies with the combination would be indicated only if preneoplastic lesions occurred at a new organ or tissue site. Classifying a lesion as preneoplastic is subjective. More general guidance on decision criteria for carcinogenicity testing of combinations of preapproved drugs would be useful. There should also be consideration of threshold and dose response in assessing the significance of a preneoplastic finding and in determining the need for combination carcinogenicity studies.

Regarding labeling and consistent with the approach taken with developmental toxicity, would a combination in which one component had a tumorigenic signal be labeled as carcinogenic without the need of conducting a combination carcinogenicity study, assuming the risk/benefit warranted consideration as a combination product?

B. Nonclinical Study Recommendations

Though implied in the preceding text, modifying the last sentence (lines 116-118) to read, "...FDA strongly recommends that sponsors conduct nonclinical studies of the combination prior to Phase 1 clinical studies to better evaluate the interaction potential (see Figure A)" would clarify expectations.

In lines 121-122 the draft guidance states, "It may be important to repeat some studies, such as equivocal reproductive toxicity studies." Given the variability inherent in many reproductive toxicity endpoints, repetition of a study may again produce equivocal results. Rather than repeat studies with the individual molecular entities, we recommend that an embryofetal development study be

conducted with the combination, and, if necessary to aid in explaining results, that a relevant dose of the single molecular entity(ies) be included.

In line 126 it is stated, "The FDA recommends that combinations studies include an assessment of several dose levels of the combination." We suggest that it be indicated "where appropriate" as depending on the data, it may be that an assessment is needed at only a single combination dose level i.e., the anticipated high clinical dose of both drugs.

Criteria for justifying selection of a single species to be used in nonclinical testing of the drug combination are given in lines 129-135. Since there is often poor concordance from animals to humans in assessing toxicity endpoints, additional guidance on species justification would be of benefit. If toxicity profiling between species is inconclusive, would justification on the basis of pharmacological mechanism be acceptable? In addition, the final sentence of the paragraph allows for an additional species to be requested based on results from the first species. This would likely cause significant delay in the clinical development of new therapeutics. We recommend that detail be added to this section and that examples be included to assist in program planning. We recommend a meeting with FDA to discuss the justification of a single species early in the development process.

C. Combinations of Previously Marketed Drug Products : General Procedure

The potential for pharmacokinetic interactions resulting from administration of combinations is discussed in lines 150-151, and boxes 4 and 5 of Figure A recommend the conduct of in vitro metabolism studies to elucidate these potential interactions. However, the in vitro metabolism package (including calculated K_i values for multiple CYP isozymes) should be available for each individual drug or NME at this point in development, and this information would be sufficient to predict the potential for a metabolic interaction between the two drugs when given in combination. Thus, the individual in vitro metabolism data packages should provide sufficient data to guide the design of clinical drug-drug interaction studies, and early clinical studies of the combination will fully characterize the pharmacokinetics of the combination.

Nonclinical toxicity studies are mentioned in lines 163-164 but no detail is provided. We suggest that a statement to the effect that nonclinical toxicology studies of scientifically appropriate duration for the clinical indication may be required and that duration up to 90 days would be required for chronic indications.

Regarding genotoxicity, in lines 173-174, and lines 197-199 and 302-307 in subsequent sections, it is stated that generally combination products will not require testing for genotoxicity if adequate testing of the individual components

has been completed. It would be helpful if the agency would state the circumstances or provide examples by which the FDA would require testing of the combination.

Requirements for reproductive and developmental toxicity studies (EFD) are described for combinations of two marketed drugs in lines 174-177 and in subsequent sections for combinations of marketed and NME (lines 218-221) and two NMEs (lines 319-322). The guidance is not clear on whether EFD studies should be conducted in one or two species as is discussed for the bridging general toxicology study. Additional comment on this point would be helpful in designing acceptable programs.

On the issue of EFD studies, we agree with the determination that developmental toxicity studies with a combination product are not needed if one drug product has demonstrated a significant developmental liability and recommend that this apply to all scenarios. As currently stated, combination studies "may not be needed" when developing a combination of two NMEs if one of the NMEs demonstrates risk. It is not clear, in this circumstance, under what conditions combination studies would be required. Furthermore, if no reproductive liabilities were identified for either drug alone and there was no scientific justification for any type of interaction from combination general toxicology or PK/ADME studies, we propose that reproductive toxicity studies of the combination would not be needed.

On lines 177-179 it should state that combination carcinogenicity studies will be indicated if preneoplastic lesions were observed at a new organ or tissue site in the toxicity study "conducted with the combination". This statement should be subject to further modification based on consideration of the comments related to characterization of preneoplastic lesions given under Section II. A. Safety Considerations.

Section III. Nonclinical Studies for a Combination of Drugs When One or More Is Previously Marketed and One Is a New Molecular Entity.

A. General Toxicology Studies

The timing of combination nonclinical studies relative to clinical trials is unclear. Although Figure B appears to indicate that studies up to 90 days are necessary prior to *any* clinical studies, the text does not (lines 201-202). Clarification on timing requirements and whether factors listed in Section II.A. apply for combinations of MD-NME and NME-NME would be of benefit.

On lines 203-206, the document recommends that "the drugs be at ratios that are relevant to the intended clinical use" when referring to a general toxicology combination bridging study for a MD-NME combination. When discussing the same type of study for a NME-NME combination on lines 263-266, the document states that "the drugs be tested at doses that produce exposure ratios that are

relevant to the intended clinical use, when feasible." It is unclear whether the consideration of "ratios" in dose selection for the general toxicology combination studies refers to clinical dose ratios (e.g. mg of drug A:mg of drug B) or, exposure ratios to provide appropriate margins of safety for each component (e.g. animal AUC:human AUC).

B. Reproductive and Developmental Toxicity

As in Section II., clarification is needed on the number of species to be used in evaluation of embryofetal development (lines 218-219). We recommend that an EFD study be conducted with the combination in rats only, unless the rabbit has been shown to be uniquely sensitive to developmental effects induced by one or more of the combination components.

C. Animal Models of Efficacy

The sections "Animal Models of Efficacy" (lines 225-228 and 277-280) describe testing combinations of MD-NME and NME-NME in animal models intended to determine whether one of the components of the combination alters the efficacy of the other component. The relevance of patho-physiologic models in assessing safety is suspect and therefore the utility of such studies are doubtful in evaluating drug combinations. We suggest these paragraphs be deleted from the guidance and if necessary the broader issue of the role of patho-physiological animal models in nonclinical safety assessment be considered separately.

Section IV. Nonclinical Studies for a Combination of Two or More Drugs When Both Are New Molecular Entities.

The timing of combination nonclinical studies relative to clinical trials is unclear. Figure C, Box 1 indicates combination studies "usually" should be conducted and to "see text for details". However, the text does not clearly indicate when combination studies are needed in relation to the timing of clinical trials. We recommend the same algorithm for all sections, which is to consider factors in section II.A to determine whether there is cause for concern.

A. General Toxicology Studies

FDA proposes that exposure ratios achieved in nonclinical combination studies be "relevant to the intended clinical use, when feasible" (lines 264-266). Determination of the optimal dosing ratio will be determined most often after extensive clinical evaluations and may not be available to design nonclinical combination studies. Further clarification on the dosing intent under these circumstances would be helpful in designing appropriate studies.

Determination of doses to employ in a combination study is highly dependent on prior knowledge from single agent repeat-dose studies. While in principle, exposures should be equal to or exceed those for maximal efficacy in patients, this may not always be tolerated in animals as suggested in lines 268-273. Therefore, we believe the doses of each agent should produce adverse effects

that the animal model can tolerate and not be dependent on human therapeutic doses. Differences in target sensitivity or metabolism are common reasons for deviations from allometric linearity. Doses of each agent should be such that they produce some degree of toxicity but that the highest selected dose not be an MTD nor an NOEL. The doses should be selected such that if additive toxicity is observed (an expected response), the effect is not lethality and the additivity can be studied. If synergy or an unexpected exaggerated response is observed, the effect should be characterized sufficiently to support further product development decisions. Negative interaction may also be seen, but while interesting, poses no additional risk for clinical development and is, therefore, less important.

B. Animal Models of Efficacy
See comments on section III.C. above.

C. Safety Pharmacology
This guidance (lines 282-288) strongly recommends the conduct of combination safety pharmacology studies, particularly in cases when both drugs target the same organ system, toxicity is associated with a particular class of compounds, or the intended patient population is compromised. We propose that safety pharmacology studies with the combination are needed only when both agents target the same organ system or physiology and then only the studies necessary to assess function in that organ system be conducted.

D. PK/ADME and Toxicokinetics
In lines 296-297 the guidance suggests that sponsors evaluate serum protein binding and monitor plasma concentrations of each drug in the toxicology studies. However, if the sponsor conducts a toxicokinetic analysis early in drug development as is suggested and is familiar with the pharmacokinetic characteristics of the combination, it would seem that additional assessment of protein binding adds negligible value.

F. Special Toxicology
In line 312 reference to testing in "a particular therapeutic area relevant to the proposed use" is unclear. In testing for safety it doesn't seem that the therapeutic area would be relevant unless the intent was to test in patho-physiologic models and as discussed previously we recommend that such testing is not warranted. It would also be helpful for FDA to provide examples of issues that might require special toxicology studies.

G. Reproductive and Developmental Toxicity
As in Section III.B., clarification is needed on the species to be used in evaluation of embryofetal development (lines 319-320). We recommend that an embryofetal development study be conducted with the combination in rats only, unless the rabbit has been shown to be uniquely sensitive to developmental effects induced by one or more of the combination components.

Figures

Figure B appears to be inconsistent with the logic as shown in both Figures A and C; thus impact of results of specific study types on decision-making is unclear. Figure B should be modified to reflect similar logic.